REMARKS

Claims 1-22 and 24-38 are pending. Claims 22, 36 and 37 have been amended for clarity. No new matter is believed to have been added by these amendments.

I. Statement of Substance of Interview

Applicants' representative Dr. William Brow thanks Examiners Welter and Channavajjala for the courteous and helpful personal interview conducted on August 10, 2011. Applicants' representative discussed the presently pending rejections. Specifically, Applicants' representative explained the fact that the presently claimed microcapsules ***require*** that the recited water soluble active ingredient is homogeneously dispersed in the recited water-insoluble coating in the claimed amounts, a feature which is neither disclosed nor suggested in the cited references. Accordingly, the present claims are patentable over the cited references.

II. Rejections under 35 U.S.C. § 103(a)

The present claims are rejected as obvious over various combinations of US 6,558,770 (*Tsuchida*); Encyclopedia of Chemical Processing and Design, "Organic Phase Separation Coacervation," pg. 167, **1989** (*McKetta*); "Pharmaceutical Dissolution Testing," Volume 49, 1992, pg. 144 (*Banakar*); US 6,120,802 (*Breitenbach*); US 4,634,587 (*Hsiao*); and US 4,704,285 (*Alderman*). Applicants respectfully traverse these rejections on the grounds that no combination of the cited references discloses all of the elements of the present claims.

Applicants' invention is directed to active ingredient-containing (i.e., drug-containing) microcapsules having relatively low levels of homogeneously dispersed drug (e.g., suitable for dosage forms requiring extremely low active ingredient concentrations). Conventional techniques are difficult, expensive, and do not provide homogeneous distributions at relatively low levels of active ingredient. *See* specification at page 2.

Applicants' claim 22 recites, *inter alia*, "[m]icrocapsules comprising: a) a core having a dimension ranging from 50 to 1200 μm; and b) a coacervated polymeric membrane coating said core comprising: 1) a water-insoluble coating polymer; and 2) at least one water-soluble

active ingredient homogeneously dispersed therein in the form of solid particles… said active ingredient being present in amounts ranging from 0.2% to 21%, with respect to the weight of the microcapsule" Accordingly, Applicants' invention requires: (1) the membrane layer is formed by coacervation, and (2) the coacervated membrane comprises a water-insoluble coating polymer and at least one water-soluble active ingredient homogeneously dispersed in said water-insoluble coating polymer in the form of solid particles, wherein the active ingredient homogeneously dispersed in the water-insoluble polymer is present in relatively low amounts ranging from 0.2% to 21%, with respect to the weight of the microcapsule. No combination of the cited references discloses or suggests all the limitations of the present 22, and accordingly, the Examiner has failed to properly establish a *prima facie* case of obviousness. As a result, Applicants respectfully request reconsideration and withdrawal of the present rejections.

A. *Tsuchida* and *McKetta*

Claims 22, 24-25 and 38 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over *Tsuchida* in view of *McKetta*. Office Action at p. 4. Applicants traverse on the ground that no combination of *Tsuchida* and *McKetta* discloses all the limitations of the present claim 22.

Tsuchida discloses multiple-unit sustained release tablets including granules comprising a matrix composed of a water-insoluble polymer and an active ingredient.[1] The resultant "matrix granules" can be further coated "with a release-controlling film."[2] Such "release-controlling films" are effective to more efficiently control the dissolution rate of the active ingredient.[3] However, each and every exemplary granule disclosed by *Tsuchida* is prepared by a coating process using a bottom-spray type fluidized bed coater.[4] In addition, *Tsuchida* is silent with respect to granules having a ***coacervated*** membrane comprising a water-insoluble coating polymer, or a coating having at least one water-soluble active ingredient ***homogeneously*** dispersed therein as required by the present claim 22. *Tsuchida* makes no explicit disclosure with respect to the amount of active ingredient in the disclosed

[1] *Tsuchida* at col. 1, ll. 60-61.
[2] *Id.* at col. 3, , ll. 13-14.
[3] *Id.* at col. 3, ll. 43-45.
[4] *Id.* at col. 5, l. 20 – col. 7, l. 45.

granules beyond relative ratios of active ingredient and polymer.[5] The following table presents the relative amounts and percentages of the various components of the exemplary matrix granules of *Tsuchida*, and the coating films thereon (where such a film is present; see Examples 3-5 of *Tsuchida*):

Table 1 of *Tsuchida* - Examples

Example	1		2		3		4		5	
Matrix Granule	g	%	g	%	g	%	g	%	g	%
Celphere	1000	50	1000	50	1000	50	1000	45	1000	49
Active	500	25	500	25	500	25	600	27	600	29
Ethyl Cellulose - 20 cps	500	25					600	27	450	22
Ethyl Cellulose - 45 cps			500	25	500	25				
Total Mass of Granule	2000	100	2000	100	2000	100	2200	100	2050	100
Coating Film										
Ethyl Cellulose	-		-		300		440		410	
Triethyl citrate	-		-		15		22		20	
Active wt% of Granule with Coating Film		N/A		N/A		22		23		24
Total Mass	2000	100	2000	100	2315	100	2662	100	2480	100

None of the examples disclosed by *Tsuchida* comprise an active ingredient present in amounts ranging from the relatively low levels claimed of 0.2% to 21% with respect to the weight of the microcapsule (see Table 1, above), and in fact, each exemplary granule of *Tsuchida* has an active content significantly higher than the presently claimed amount (Examples 1-3: 25%; Example 4: 27%; Example 5: 29%; *see* Table 1, above).

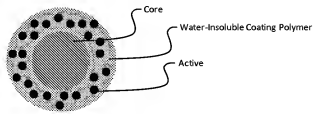
The Examiner states "if one includes the ethyl cellulose coating film in example 4 (see Table 4 of Tsuchida),[6] the drug concentration is in an amount of 22 wt.%." Office Action at p. 11. Applicants submit that this assertion ignores the plain language of the present claim 22, and disregards *Tsuchida's* characterization of the second ethyl cellulose coating film as a separate "release-controlling film." Specifically, claim 22 recites a

[5] *Id.* at col. 3, ll. 33-37.

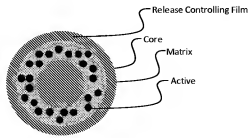
[6] Applicants note that Table 4 of *Tsuchida* does not relate to the composition of the exemplary granules of *Tsuchida*. Accordingly, Applicants assume for the present discussion the Examiner meant to refer to Table 1 of *Tsuchida*, which relates to the composition of the exemplary granules of *Tsuchida*).

coacervated polymeric membrane comprising the water insoluble polymer and a homogeneously dispersed water soluble active ingredient present in an amount of from 0.2 to 21%. First, since *Tsuchida* clearly teaches that the "matrix" containing the active ingredient, and the "release-controlling film" are two different layers, Applicants submit one cannot reasonably reinterpret *Tsuchida's* plain language so as to consider the combination of these two separate layers to be a single layer. Even if it were proper to consider the combination of *Tsuchida's* "matrix" and "release-controlling film" to be a single layer (which it is not), the active ingredient would not be homogeneously dispersed in such a composite "layer", as required by the present claim 22, since the disclosed "release-controlling films" of *Tsuchida* do not contain any active ingredient. In other words, the Examiner's proposed combination would provide *inhomogeneously* distributed active ingredient, since it would only be present in the "matrix" portion of the proposed composite "layer". The diagram below provides a graphical representation of an embodiment of the claimed microcapsule, and the granule of *Tsuchida*, including the release-controlling film (as proposed by the Examiner).

Claimed Microcapsule

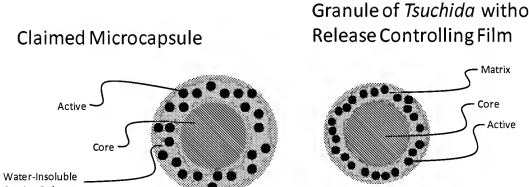


Granule of *Tsuchida* with Release Controlling Film



As shown in the above figure, inclusion of the coating film of Example 3 of *Tsuchida* as proposed by the Examiner would not provide a homogeneously dispersed active ingredient in the water-insoluble coating polymer as ***required*** by the present claim 22.

Furthermore, as shown in the figure below, if one were to remove the release-controlling film of *Tsuchida*, the resultant granule is substantively different from the presently claimed microcapsules. For example, the granule has a significantly higher concentration of active relative to the presently claimed microcapsule (*e.g.*, at least 25%, *supra*). Thus, the Examiner's rationale and proposed inclusion of the release controlling film of *Tsuchida* actually emphasizes the differences between the microgranules of Tsuchida and the presently claimed microcapsules.



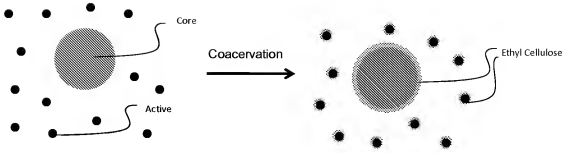
Further, the Examiner asserts that a *prima facie* case of obviousness exists where the claimed ranges and prior art ranges do not overlap but are close enough that one skilled in the art ***would have expected them to have the same properties***. Office Action at p. 6, citing *Titanium Metals Corp. of America v. Banner*, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985); emphasis added. Applicants submit that this rationale is defective. It is not clear how one skilled in the art would expect the microcapsules of *Tsuchida*, which comprise different amounts of active ingredient relative to the presently claimed microcapsules, to have the same properties (e.g., dissolution rate, pharmacokinetic parameters, etc.). In the instant case, Applicants' claimed invention requires a lower limit on the active ingredient concentration and the Examiner has provided no reference to support the proposition that the higher

concentration suggested by *Tsuchida* would have the same properties as Applicants.. Accordingly, Applicants submit that the Examiner's assertion that the presently claimed microcapsules and those described by *Tsuchida* would be expected to have the same properties is incorrect, and one skilled in the art of pharmaceutical formulations would not expect that the formulations described by *Tsuchida*, which are significantly different from that presently claimed, would have the same properties. Thus, the granules of *Tsuchida*, either with or without the release controlling film, are substantively different from the presently claimed microcapsules, and accordingly, *Tsuchida* fails to suggest the presently claimed microcapsules.

McKetta fails to remedy the deficiencies of *Tsuchida*.

McKetta fails to describe a water insoluble polymer membrane having a water insoluble active ingredient *homogeneously* dispersed therein. Rather, *McKetta* teaches coacervation as a method of coating small particles with ethyl cellulose known in the pharmaceutical industry. However, *McKetta* is silent with respect to coacervation of a membrane ***including solid particles of a water-soluble active ingredient***, much less a membrane having the solid particles of water-soluble active ingredient homogeneously dispersed therein as required by the present claims. The Examiner has failed to provide any articulated reasoning as to how one of ordinary skill in the art, relying on *McKetta*, who describes solvent coacervated coatings consisting ***only*** of ethyl cellulose, would glean how to produce the present solvent-coacervated polymeric membrane comprising a water-insoluble coating polymer having a solid particles of a water-soluble active ingredient, much less how to achieve a homogenous dispersion of the active ingredient therein.

In fact, by the Examiner's proffered rationale, since *McKetta* teaches coacervation as a method of coating small particles, and the cores and particles of active ingredient recited in the present claim 22 are both small particles, one skilled in the art could reasonably expect that solvent-coacervation of a mixture of cores and solid particles of active ingredient would produce a mixture of membrane-coated cores and membrane-coated solid particles of active, as shown in the figure below.



Thus, *McKetta* fails to remedy the deficiencies of *Tsuchida*, and no combination of *Tsuchida* and *McKetta* discloses or suggests all the limitations of the presently claimed microcapsules. Therefore, the Examiner has failed to establish a *prima facie* case of obviousness. As a result, the present rejection is improper, and should be withdrawn.

B. *Tsuchida, McKetta* and *Banakar*

Claims 33-34 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over *Tsuchida* in view of *McKetta*, and in further view of *Banakar*. Applicants traverse on the ground that no combination of *Tsuchida, McKetta* and *Banakar* discloses all the limitations of the present claim 22.

As discussed above, no combination of *Tsuchida* and *McKetta* discloses or suggests all the limitations of the presently claimed microcapsules. *Banakar* fails to remedy the deficiencies of *Tsuchida* and *McKetta*.

Banakar relates to active particle size in drug formulations. However, *Banakar* is silent with respect to microcapsules having a membrane formed by coacervation, much less microcapsules as recited in the present claims having (1) a membrane layer formed by coacervation, and (2) an active ingredient present in amounts ranging from 0.2% to 21% with respect to the weight of the microcapsule homogeneously dispersed in the membrane. Therefore, *Banakar* fails to remedy the deficiencies of *Tsuchida* and *McKetta* with respect to the present claims, and no combination of *Tsuchida*, *McKetta* and *Banakar* discloses or suggests the present microcapsules. Thus, the Examiner has failed to properly establish a *prima facie* case of obviousness. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

C. *Tsuchida, McKetta* and *Breitenbach*

Claim 35 is rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over *Tsuchida* in view of *McKetta,* and in further view of *Breitenbach.* Applicants traverse on the ground that no combination of *Tsuchida, McKetta* and *Breitenbach* discloses all the limitations of the present claim 22.

As discussed above, no combination of *Tsuchida* and *McKetta* discloses or suggests all the limitations of the presently claimed microcapsules. *Breitenbach* fails to remedy the deficiencies of *Tsuchida* and *McKetta.*

Breitenbach discloses a process for producing multilayer, solid drug forms for oral or rectal administration, which comprises coextrusion of at least two compositions which in each case comprise a thermoplastic, pharmacologically acceptable polymeric binder which is soluble or swellable in a physiological environment, and at least one of which contains a pharmaceutical active ingredient, and shaping the coextruded multilayer material to the required drug form.[7]

However, *Breitenbach* is silent with respect to microcapsules having a membrane formed by coacervation, much less microcapsules as recited in the present claims having (1) a membrane layer formed by coacervation, and (2) an active ingredient present in amounts ranging from 0.2% to 21% with respect to the weight of the microcapsule homogeneously dispersed in the membrane. Therefore, *Breitenbach* fails to remedy the deficiencies of *Tsuchida* and *McKetta* with respect to the present claims, and no combination of *Tsuchida, McKetta* and *Breitenbach* discloses or suggests the present microcapsules. Thus, the Examiner has failed to properly establish a *prima facie* case of obviousness. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

D. *Tsuchida, McKetta, Hsiao* and *Alderman*

Claim 35 is rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over

[7] *See* Abstract of *Breitbach.*

Tsuchida in view of *McKetta,* and in further view of *Hsaio* and *Alderman*. Applicants traverse on the ground that no combination of *Tsuchida, McKetta, Hsiao* and *Alderman* discloses all the limitations of the present claim 22.

Hsiao discloses a sustained release quinidine dosage form made from a plurality of pellets, each pellet including a quinidine containing coating over a nonpareil seed, with ***a further coating*** (*i.e.*, on top of the active) of about 5 to about 15% by weight of a mixture of about 1.5 to about 9 parts by weight ethylcellulose to about 1 part by weight hydroxypropylcellulose.[8] However, *Hsiao* is silent with respect to coacervation. In addition, the pellets disclosed by *Hsiao* are coated with ***more than*** an equal amount by weight of active (*i.e.*, quinidine) compound.[9] Thus, *Hsiao* fails to disclose microcapsules having a membrane formed by coacervation, much less microcapsules as recited in the present claims having (1) a membrane layer formed by coacervation, and (2) an active ingredient present in amounts ranging from 0.2% to 21% with respect to the weight of the microcapsule homogeneously dispersed in the membrane. Therefore, *Hsiao* fails to remedy the deficiencies of *Tsuchida* and *Mcketta* with respect to the present claims.

Alderman fails to remedy the deficiencies of *Tsuchida, McKetta* and *Hsiao.*

Alderman discloses solid tablets of a therapeutically active composition which exhibit sustained release properties when compressed with a fine particle sized hydroxypropyl cellulose ether composition.[10] However, *Alderman* is silent with respect to microcapsules having a membrane formed by coacervation, much less microcapsules as recited in the present claims having (1) a membrane layer formed by coacervation, and (2) an active ingredient present in amounts ranging from 0.2% to 21% with respect to the weight of the microcapsule homogeneously dispersed in the membrane. Therefore, *Alderman* fails to remedy the deficiencies of *Tsuchida, McKetta* and *Hsiao* with respect to the present claims, and no combination of *Tsuchida, McKetta, Hsiao* and *Alderman* discloses or suggests the present microcapsules. Thus, the Examiner has failed to properly establish a *prima facie* case of obviousness. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

---

[8] *See* Abstract of *Hsiao*; emphasis added.
[9] *See Hsiao* at col. 1, ll. 27-30; emphasis added.
[10] See Abstract of *Alderman*.

Finally, Applicants note that the secondary references cited against the dependent claims do not teach or suggest the narrowing limitations as presently claimed. First, the Examiner apparently argues that *Breitenbach* teaches the limitation "the coating polymer varies from 2 to 20% by weight of the microcapsule" in dependent claim 35. *Breitenbach*, however, does not expressly state such a range of a coating polymer in a microcapsule or drug form whatsoever, nor does it provide an example or embodiment with a coating polymer that is within the claimed range. Accordingly, *Breitenbach* does not teach or suggest the specific range of a coating polymer as presently claimed in claim 35.

The Examiner also apparently argues that *Hsiao* and *Alderman* teach the limitations of adding additives having a diameter range as in dependent claims 36 and 37 (0.1 to 80 μm; 7 to 30 μm respectively) and an additive with a % by weight range of the microcapsule (2 to 10% by weight; 3% to 5% by weight respectively). First, *Hsiao* does not provide even one example that suggests including an additive within the claimed % by weight range of the microcapsule: Example 1 is silent regarding % by weight; Example 2 provides 0.6% by weight of hydroxpropylcellulose; Example 3 provides 1.0 % by weight of hydroxpropylcellulose; and Example 4 provides 1.4 % by weight of hydroxpropylcellulose. Also, *Hsiao* is silent regarding the diameter of any additives as presently claimed in dependent claims 36-37.

Second, *Alderman* does suggest including additives to a coating. *Alderman* teaches solid tablets comprising hydroxypropylcellulose ether in the core, not in the membrane coating.[11] Also, the preferred amount of hydroxypropylcellulose ether in *Alderman* is 40 to 80 percent by weight, much higher than the 2% to 10% by weight as presently claimed in claim 36, and the 3% to 5% by weight in claim 37.[12] Accordingly, the combination of *Hsiao* and *Alderman*(which were cited solely against dependent claims 36-37) do not teach or suggest these limitations as presently claimed.

[11] *See, e.g.*, Alderman, col. 1, l. 64 – col. 2, l. 6.
[12] *See Alderman*, col. 2, ll. 33-35.

II. Conclusion

Applicants respectfully submit that the claims are now in condition for allowance, early notice of which would be appreciated. Should the Examiner disagree, Applicants respectfully request a telephonic or in-person interview with the undersigned attorney to discuss any remaining issues and to expedite the eventual allowance of the claims.

Except for issue fees payable under 37 C.F.R. 1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-1283. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. 1.136(a)(3).

Dated: November 14, 2011

Respectfully submitted,
COOLEY LLP

COOLEY LLP
CUSTOMER NUMBER 91543
ATTN: Patent Group
777 6th Street, NW, Suite 1100
Washington, DC 20001
Tel: (202) 842-7889
Fax: (202) 842-7899

By: /Thomas A. Blinka/
Thomas A. Blinka, Ph.D.
Reg. No. 44,541